

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claims 1-21. (Cancelled).

22. (Currently Amended): A method of inserting a ~~heterologous gene coding sequence~~ gene of interest into an endogenous gene in a mouse embryonic stem cell ~~genome and expressing said heterologous gene coding sequence, comprising the step of~~ such that the gene of interest is expressed in said mouse embryonic stem cell, wherein said method comprises transforming the mouse embryonic stem cell with a random gene trap vector comprising a DNA construct, wherein the heterologous gene coding sequence lacks a promoter, and (ii) comprises the sequence:

5' ——— X A P B Q C Y ——— 3'

in which

——— X and Y ——— are separately, DNA sequences substantially homologous with a host gene locus;

a heterologous gene coding sequence: 5' X-A-P-B-Q-C-Y-3' wherein:

X and Y are substantially homologous with separate sequences of the endogenous gene, and are of sufficient length to undergo homologous recombination with the endogenous gene so as to insert the A-P-B-Q-C elements into the host cell's genome;

P is an internal ribosome entry site (IRES);

Q is the heterologous gene of interest sequence, including a translation start codon; and;

A, B, and C are, separately, optional linker sequences each independently at least one of a linker sequence and a covalent bond;

a polyadenylation site is located 3' (downstream) of Q;

a splice acceptor site is located 5' (upstream) of P; and

wherein the heterologous gene coding sequence lacks a promoter element.

~~wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of P.~~

23. (Currently Amended): ~~A~~ The method of ~~according to~~ Claim 22 where the heterologous gene coding sequence is randomly inserted into an endogenous gene so that transcription of the heterologous gene coding sequence is directed by the host regulatory elements of the endogenous gene.

24. (Currently Amended): ~~A~~ The method of ~~according to~~ Claim Claim 22 in which the splice acceptor permits functional integration of the heterologous gene coding sequence into an intron sequence.

Claim 25. (Cancelled).

26. (Currently Amended): ~~A~~ The method of ~~according to~~ Claim 22 further comprising the step of identifying cells expressing the heterologous gene coding sequence.

27. (Currently Amended): ~~A~~ The method of ~~according to~~ Claim 26 wherein the construct also comprises a gene encoding a selectable marker and the method comprises selecting cells that express the selectable marker.

Claims 28-31. (Cancelled).

32. (Currently Amended): A DNA construct for ~~randomly~~ inserting a gene of interest ~~heterologous gene sequence~~ into a mouse cell genome, ~~said heterologous gene sequence lacking a promoter and comprising~~ wherein said DNA construct comprises a heterologous gene sequence which lacks a promoter element and which comprises the sequence:

5' X-A-P-B-Q-C-Y 3'

~~in which~~

~~———— X and Y ————— are separately, DNA sequences substantially homologous with a host gene locus;~~

wherein:

X and Y are substantially homologous with separate sequences of an endogenous gene, and are of sufficient length to undergo homologous recombination with the endogenous gene so as to insert the A-P-B-Q-C elements into the mouse cell's genome;

P is an internal ribosome entry site (IRES);

Q is a gene of interest ~~the heterologous gene sequence, including a translation start codon ; and~~

A, B and C are each independently at least one of a linker sequence and a covalent bond , separately, optional linker sequence[s];

a polyadenylation site is located 3' (downstream) of Q; and

a splice acceptor site is located 5' (upstream) of P.

~~wherein the DNA construct further comprises a polyadenylation signal at the 3' (downstream) end of Q and a splice acceptor site located 5' (upstream) of P.~~

33. (Currently Amended): The DNA construct of A ~~DNA construct according to~~ Claim 32 in which the splice acceptor permits functional integration of the heterologous gene into an intron sequence.

34. (Currently Amended): The DNA construct of A ~~DNA construct according to~~ Claim 32 in which the construct also comprises a gene encoding a selectable marker to facilitate selection of mouse cells containing a heterologous gene that has been inserted into an endogenous gene.

Claims 35-40. (Cancelled).

41. (Currently Amended): The method of A ~~method according to~~ Claim 22 wherein the construct also comprises a gene encoding antibiotic resistance, and the method comprises selecting cells that express the antibiotic resistance.

42. (Currently Amended): The DNA construct of A ~~DNA construct according to~~ Claim 32 wherein the construct additionally comprises a gene encoding antibiotic resistance.

Claims 43-72. (Cancelled).

73. (Currently Amended): A DNA construct for inserting a heterologous gene ~~coding~~ sequence into a target ~~endogenous~~ gene in the genome of a eukaryotic ~~cellular host cell~~ genome, wherein the said DNA construct comprises the elements: the heterologous gene sequence which comprises the sequence:

5' X-A-P-B-Q-C-Y 3' wherein:

~~in which~~

X and Y are substantially homologous with separate sequences of the ~~from the target~~ endogenous gene, and are of sufficient length to undergo homologous recombination with the ~~host cell genome~~ endogenous gene so as to insert the A-P-B-Q-C elements into the ~~host cell genome~~ of the host cell;

P is an internal ribosome entry site (IRES);

Q is ~~the heterologous gene coding sequence~~ a gene of interest; and

A, B, and C are ~~, separately, linker sequence or a covalent bond~~ each independently at least one of a linker sequence and a covalent bond.

74. (Currently Amended): The DNA construct ~~according to~~ of Claim 73, wherein the construct also comprises a gene encoding a selectable marker.